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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 6 : C07D 473/06, A61K 31/52, G01N 33/06, 33/60 — A1

(11) International Publication Number: **WO 98/22465**

(43) International Publication Date: 28 May 1998 (28.05.98)

(21) International Application Number: PCT/US97/21045

(22) International Filing Date: 19 November 1997 (19.11.97)

(30) Priority Data:
08/753,048 19 November 1996 (19.11.96) US

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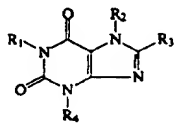
(81) Designated States: AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, ES, FI, GB, GE, GH, HU, ID, IL, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, UA, UG, US, UZ, VN, YU, ZW, ARIPO patent (GH, KE, LS, MW, SD, SZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Published
With international search report.
Before the expiration of the time limit for amending the claims and to be republished in the event of the receipt of amendments.

(54) Title: A_1 ADENOSINE RECEPTOR ANTAGONISTS



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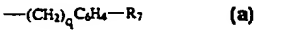

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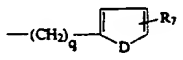

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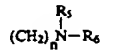

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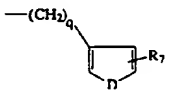

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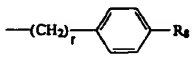

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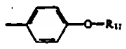

(d)

(57) Abstract

A compound useful as an A_1 adenosine receptor antagonist has formula (I), wherein R_1 is selected from the group consisting of C_1–C_8alkyl; R_2 is of formula (II), wherein n is an integer ranging from 1 to 8; R_5 is H or $CH_3(CH_2)_p$, wherein p is an integer ranging from 1 to 7; and R_6 is H; $(CH_2)_mH$; or $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8; R_3 is selected from the group consisting of: (a), (b), (c) and (d), wherein q is an integer ranging from 1 to 8; D is selected from the group consisting of NH, S, and O; wherein R_7 is selected from the group consisting of H, OH, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; R_{11} is selected from the group consisting of $-CH_2COOH$ and $-CH_2-CONH(CH_2)_wNHZ$, wherein w is an integer ranging from 1 to 2 and Z is selected from the group consisting of hydrogen and acetate; and R_4 is of formula (III), wherein R_8 is selected from the group consisting of H; OH; $(CH_2)_fNH_2$ wherein f is selected from the group consisting of 0 and an integer ranging from 1 to 8; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8.

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A_1 ADENOSINE RECEPTOR ANTAGONISTS

Cross-Reference to Related Applications

The instant application is a continuation-in-part application of U.S. Patent Application Serial No. 08/753,048 filed November 19, 1996.

Field and Background of the Invention

The present invention relates to novel compounds useful as A_1 adenosine receptor antagonists.

Adenosine receptors are involved in a vast number of peripheral and central regulatory mechanisms such as, for example, vasodilation, cardiac depression, inhibition of lipolysis, inhibition of insulin release and potentiation glucagon release in the pancreas, and inhibition of neurotransmitter release from nerve endings.

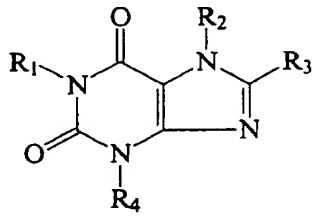
In general, adenosine receptors can be divided into two main classes, A_1 receptors which can inhibit, and A_2 receptors which can stimulate adenylate cyclase activity. One of the best known classes of adenosine receptor antagonists are the xanthines which include caffeine and theophylline. See e.g., Müller et al., *J. Med. Chem.* 33: 2822-2828 (1990). In general, many of these antagonists often suffer from poor water solubility, and low potency or lack of selectivity for adenosine receptors.

Additionally, selective analogues of adenosine receptor antagonists have been developed through the "functionalized congener" approach. Analogues of adenosine receptor ligands bearing functionalized chains have been synthesized and attached covalently to various organic moieties such as amines and peptides. Attachment of the polar groups to xanthine congeners has been found to increase water solubility. Nonetheless, such developments have yet to fully address problems associated with potency and selectivity. More recently Jacobson et al. *J. Med. Chem.* **35**: 408-422 (1992) has proposed various derivatives of adenosine and theophylline for use as receptor antagonists. The article discloses that hydrophobic substituents are able to potentially enhance affinity. However, it is also acknowledged that such substituents may result in a decrease in solubility thus rendering the antagonists less soluble *in vivo*. In confronting these problems, Jacobson et al. indicates that a dipropyl substitution at the 1 and 3 positions of theophylline allows desirable affinity at A_1 receptors. It is also stated that substitutions at the 7-position are typically not favorable.

It is an object of the present invention to therefore provide compounds useful as A_1 adenosine receptor antagonists which display high potency and affinity levels, along with water solubility.

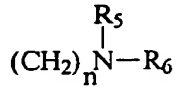
Summary of the Invention

In one aspect, the present invention provides a compound of the general formula:



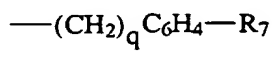
wherein R_1 is selected from the group consisting of C_1-C_8 alkyl;

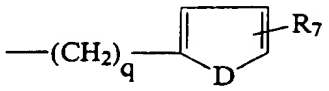
R_2 is of the formula:

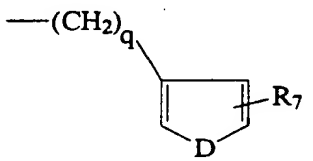


wherein n is an integer ranging from 1 to 8; R_5 is H or $CH_3(CH_2)_p$, wherein p is an integer ranging from 1 to 7; and R_6 is H, $(CH_2)_mH$, or $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8;

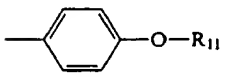
R_3 is selected from the group consisting of:







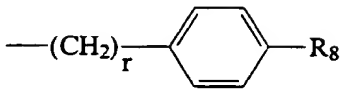
and



wherein q is an integer ranging from 1 to 8; D is selected from the group consisting of S, NH, and O; and wherein R_7 is selected from the group consisting of H, OH, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; wherein R_{11} is selected from the group consisting of $-CH_2COOH$ and $-CH_2\text{-}CONH(CH_2)_wNHZ$, wherein w is an

integer ranging from 1 to 2 and Z is selected from the group consisting of hydrogen and acetate; and

R_4 is of the formula:



wherein R_8 is selected from the group consisting of H; OH; $(CH_2)_fNH_2$ wherein f is selected from the group consisting of 0 and an integer ranging from 1 to 8; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8.

In a second aspect, the invention provides for assay-type probes of the above compound, wherein the probes are marked or conjugated with radioactive or non-radioactive material.

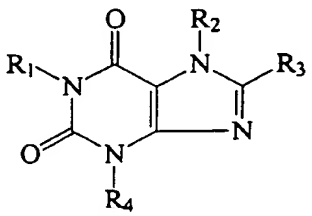
In a third aspect, the invention provides a pharmaceutically acceptable salt of the above compound.

In a fourth aspect, the invention provides a pharmaceutical composition which comprises the above compound and a pharmaceutically acceptable carrier.

Detailed Description of the Invention

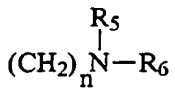
The present invention will now be described more fully hereinafter, in which preferred embodiments of the invention are shown. This invention may, however, be embodied in different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure will be thorough and complete, and will fully convey the scope of the invention to those skilled in the art.

The present invention is directed to a compound of the formula (I):



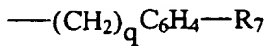
R_1 is selected from the group consisting of C_1-C_8 alkyl, preferably C_1 to C_4 alkyl. For the purposes of the invention, R_1 is more preferably C_1 or C_3 alkyl, and is most preferably C_3 alkyl.

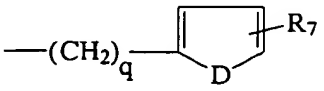
R_2 is of the formula:

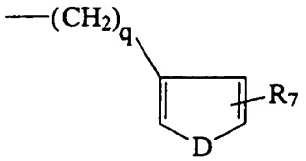


wherein n is an integer ranging from 1 to 8, more preferably 1 to 4; R_5 is H or $CH_3(CH_2)_p$, wherein p is an integer ranging from 1 to 7, more preferably 1 to 4; and R_6 is H, $(CH_2)_mH$, or $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8, more preferably 1 to 4.

R_3 is selected from the group consisting of:







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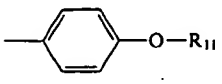
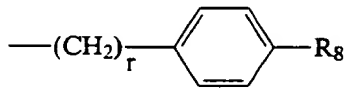


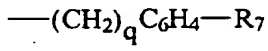
wherein q is an integer ranging from 1 to 8; D is selected from the group consisting of S, O, and NH; and wherein R_7 is selected from the group consisting of H, OH, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8. The alkylene or alkenylene groups may be substituted or unsubstituted. R_9 is preferably CH=CH. R_{11} is selected from the group consisting of $-CH_2COOH$ and $-CH_2\text{-}CONH(CH_2)_wNHZ$, wherein w is an integer ranging from 1 to 2 and Z is selected from the group consisting of hydrogen and acetate.

R_4 is of the formula:



wherein R_8 is selected from the group consisting of H; OH; $(CH_2)_fNH_2$, wherein f is selected from the group consisting of 0 and an integer ranging from 1 to 8; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8, more preferably 1 to 4; and $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8, more preferably 1 to 4. In the above, R_9 and R_{10} are preferably CH=CH.

The invention may be illustrated below with respect to preferred embodiments. In these embodiments, R_3 is of the formula:



In one preferred embodiment, R_1 is C_3 alkyl; R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is $(CH_2)_mOH$ wherein m is 2; R_7 is H; R_8 is NH_2; f is 0; n is 2; m is 2; q is 1; and r is 2.

In another preferred embodiment, R_1 is C_3 alkyl; R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is NH_2; R_8 is NH_2; f is 0; n is 2; q is 1; and r is 2.

In another preferred embodiment, R_1 is C_3 alkyl; R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is H; R_8 is NH_2; f is 0; n is 2; q is 1; and r is 2.

In another preferred embodiment, R_1 is C_3 alkyl; R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is H; R_8 is selected from the group consisting of $(CH_2)_sOH$, wherein s is 2 and $R_{10}COOH$, wherein R_{10} is CH=CH; n is 2; q is 1; and r is 2.

In another preferred embodiment, R_1 is C_3 alkyl; R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is selected from the group consisting of R_9COOH, wherein R_9 is CH=CH and $(CH_2)_tOH$, wherein t is 2; R_8 is NH_2; f is 0; n is 2; q is 1; and r is 2.

The compound of the present invention may form pharmaceutically acceptable salts with both organic and inorganic acid and bases. Examples of suitable acids for salt formation are hydrochloric, sulfuric, phosphoric, acetic, citric, oxalic, malonic, salicylic, ascorbic, maleic, methanesulfonic, and the like. Any of the amine acid addition salts may also be used. The salts are prepared by contacting the free base form of the compound with an appropriate amount of the desired acid in a manner known to one skilled in the art. Examples of suitable bases for salt formation are sodium hydroxide, sodium carbonate, sodium bicarbonate, potassium hydroxide, calcium hydroxide, ammonia, organic amines, and the like. The salts may be prepared by contacting the free acid form of the compound with an appropriate amount of the desired base in a manner known to one skilled in the art.

The invention also provides A_1 adenosine receptor antagonist compounds with radioactive or non-radioactive labels. Such labelled compounds are useful as assay-type probes or conjugates, and may be used to obtain quantitative binding measurements of the A_1 adenosine receptor antagonist compounds. For the purposes of the invention, "assay-type probes" refers to those materials which are useful for enhancing the selectivity of the quantitative analysis of the A_1 adenosine receptor compounds of the invention. Examples of such assay-type probes are described in U.S. Patent No. 5,248,770 to Jacobson et al., the disclosure of which is incorporated herein by reference in its entirety. The probes are highly useful in that they have little adverse effect on the affinity of the compounds of the present invention. Radioactive markers include, but are not limited to, an electric spin marker, a ^{19}F NMR probe, a radioactive ^{18}F

isotope marker, a radioactive iodine marker (e.g., ^{125}I), a radioactive ^{3}H marker, tritium, and a complex of a metal atom or a metal ion and a chelating agent. An exemplary metal ion is a radioactive isotope of technetium or indium. An exemplary chelating agent is diethylene pentacetic anhydride.

Various non-radioactive materials may be used in labelling the present A_1 adenosine receptor compounds. Numerous examples are presented in U.S. Patent No. 5,248,770 to Jacobson et al. Biotin is used as a common non-radioactive label for such probes, as described in R.W. Old et al. *Principals of Gene Manipulation*, **4th ed**: 328-331 (1989). To facilitate labelling the compounds with biotin or any other appropriate material, a spacer component may be added to the compound according to an accepted method. Such a method is described in the Jacobson et al. '770 patent. Exemplary spacer components include, but are not limited to, an oligopeptide, triglycidyl, and N-hydroxysuccinimide ester.

Biotin may be bonded to any suitable linkage provided by substituents on the compound structure in accordance with any accepted and suitable technique. For example, referring to compound (I) as defined herein, biotin may be bonded to the hydroxy group on R_6 when the compound contains $(CH_2)_mOH$ at R_6 with m defined herein; to the amino group present on either of R_7 or R_8 when $(CH_2)_fNH_2$ is contained at the R_8 position, wherein f is defined herein; to the hydroxyl group present as R_7 or R_8; or to the carboxyl group present when R_7 and R_8 are R_9COOH or $R_{10}COOH$ respectively, with R_9 and R_{10} defined herein. Additionally, the biotin may be bonded to a hydroxyl group present on R_8, when R_8 is $(CH_2)_sOH$ with s being defined herein. Biotin may also be bonded to R_7, when R_7 is $(CH_2)_tOH$ with t being defined herein. The biotin-labeled probes may be detected through appropriate and known analytical techniques.

Fluorescent dyes may also be employed as a non-radioactive labels and are applied to appropriate locations on the compounds of the invention. Such dyes include, but are not limited to, tetramethylrhodamine, fluorescein isothiocyanate, and mixtures thereof. Other non-radioactive materials include for example, nitrobenzoxadiazole; 2,2,6,6-tetramethyl-piperindinyloxy-4-isothiocyanate; and mixtures thereof.

The invention is also directed to a pharmaceutical composition which includes the compound of the present invention and a pharmaceutically acceptable carrier. The pharmaceutical composition is particularly useful in applications relating to organ preservation *in vivo* or *in situ*, perfusion of an isolated organ either removed or contained within the body (e.g., when an organ is transported for transplantation), cardiopulmonary bypass, perfusion of an extremity or limb, and the like. The compounds may be used in intra-articular, intra-thecal, gastrointestinal, and genital urinary applications, as well as in any cavity or lumen such as, for example, the thoracic cavity or ear canal.

The pharmaceutical composition may be employed, as an example, in oral dosage form as a liquid composition. Such liquid compositions can include suspension compositions or syrup compositions and can be prepared with such carriers as water; a saccharide such as sucrose, sorbitol, fructose, and the like; a glycol such as polyethyleneglycol, polypropyleneglycol, and the like; an oil such as sesame oil, olive oil, soybean oil, and the like; an antiseptic such as p-hydroxy- benzoic acid esters and the like; and a flavor component such as a fruit flavor or a mint flavor. The pharmaceutical composition may also be in the form of powder, pills, capsules, and tablets and can be prepared with various carriers. Suitable carriers include, but are not limited to, lactose, glucose, sucrose, mannitol, and the like; disintegrators such as starch, sodium alginate, and the like; binders such as polyvinyl alcohol, hydroxypropyl cellulose, gelatin, and the like; surfactants such as, for example, fatty acid esters; and plasticizers such as, for example, glycerins. The composition of the present invention is especially useful when applied sublingually. It should be noted that in the preparation of the tablets and capsules, a solid pharmaceutical carrier is used. Advantageously, the pharmaceutical composition may be used in the form of, for example, eye drops or an aerosol.

Other types of pharmaceutical compositions may be employed in the form of a suppository, a nasel spray, and an injectable solution. These compositions are prepared using appropriate aqueous solutions which may include, but are not limited to, distilled water, and saline and buffer additives. Other components may be employed such as organic materials

including neutral fatty bases. Additionally, the pharmaceutical composition may be utilized in a transdermal application.

Biopolymers may be used as carriers in the above pharmaceutical compositions. Exemplary biopolymers may include, for example, proteins, sugars, or lipids.

The A_1 receptor antagonists of the present invention are particularly useful as, for example, anti-allergenics, CNS stimulants, diuretics, anti-asthmatics, and cardiotonics.

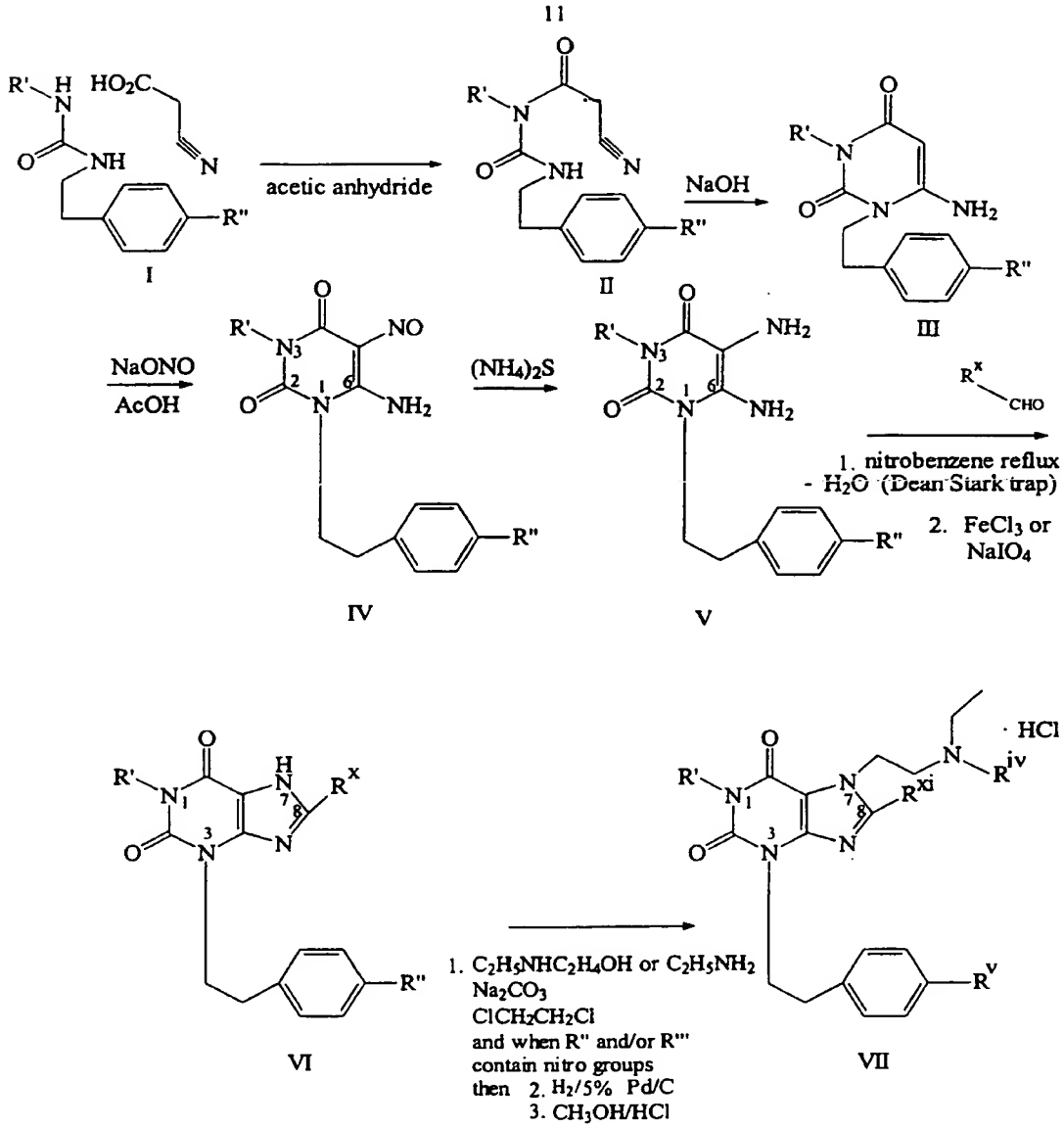
Selective analogues of adenosine receptor antagonists have been developed through the "functionalized congener" approach. See e.g., U.S. Patent No. 4,968,672 to Jacobson et al.; and Jacobson et al., *Mol. Pharmacol.* **29**: 126-133 (1985). In terms of pharmacology, the compounds advantageously display increased affinity at A_1 receptor sites relative to former A_1 receptor antagonists while simultaneously exhibiting good water solubility.

The foregoing example is illustrative of the present invention, and is not to be construed as limiting thereof.

Example

Synthesis of A_1 Adenosine Receptor Antagonists

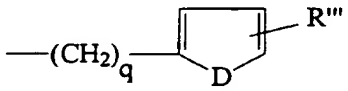
A_1 adenosine receptor antagonists of the present invention may be synthesized according to the process illustrated below:

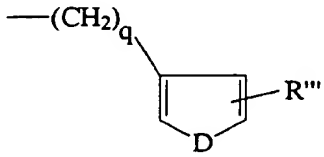


I II III IV V VI VII

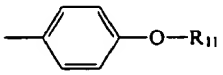
In the above reaction pathway, R' may be C_1-C_8 alkyl; R" may be selected from the group consisting of H, OH, $(CH_3)_eNO_2$ wherein e is selcted from the group consisting of 0 and an integer ranging from 1 to 8; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atom; R^x may be selected from the group consisting of:

$$(CH_2)_qC_6H_4R'''$$





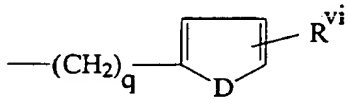
and

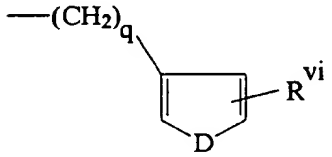


wherein R''' may be selected from the group consisting of H, OH, NO_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; D may be selected from the group consisting of O, S, and NH; q is an integer ranging from 1 to 8; R_{11} is selected from the group consisting of $-CH_2COOH$ and $-CH_2$-$CONH(CH_2)_wNHZ$, wherein w is an integer ranging from 1 to 2 and Z is selected from the group consisting of hydrogen and acetate; and R^{iv} may be selected from the group consisting of H, $(CH_2)_mH$, and $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8. As identified in formula (VII), R^v may be selected from the group consisting of H; OH; $(CH_2)_fNH_2$ wherein f is selected from the group consisting of 0 and an integer ranging from 1 to 8; $(CH_2)_sOH$, wherein s is an integer ranging

from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atoms. R^{xi} may be selected from the group consisting of:

$(CH_2)_qC_6H_4R^{vi}$





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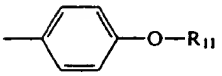


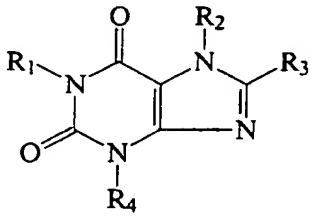
wherein D may be selected from the group consisting of O, S, and NH; q is an integer ranging from 1 to 8; R^{vi} may be selected from the group consisting of H, OH, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is

an integer ranging from 1 to 8. R_{11} is selected from the group consisting of $-CH_2COOH$ and $-CH_2-CONH(CH_2)_wNHZ$, wherein w is an integer ranging from 1 to 2 and Z is selected from the group consisting of hydrogen and acetate. In general, the above synthesis steps may be carried out at standard temperature and pressure conditions, optionally under reflux. An exception to this pertains to the reaction involving intermediates (VI) and (VII) which is preferably performed at a temperature ranging from about 25°C to about 50°C and at atmospheric pressure. In the reaction step involving intermediate (V) becoming intermediate (VI), it is desired to employ an oxidation step with $FeCl_3$ or $NaIO_4$ subsequent to the nitrobenzene reflux. Moreover, it should be noted that when R" and/or R'" contain nitro groups, a reaction step which involves applying H_2 over a Pd/C catalyst is employed prior to the reaction with CH_3OH/HCl. The resulting product (VII) may be further processed and purified according to accepted procedures.

In the specification and example, there have been disclosed typical preferred embodiments of the invention and, although specific terms are employed, they are used in a generic and descriptive sense only and not for purposes of limitation of the scope of the invention being set forth in the following claims.

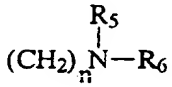
That Which is Claimed Is:

1. A compound of the formula:



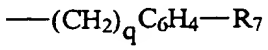
wherein R_1 is selected from the group consisting of C_1-C_8 alkyl;

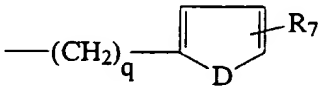
R_2 is of the formula:

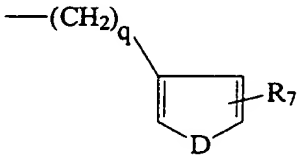


wherein n is an integer ranging from 1 to 8; R_5 is H or CH_3 $(CH_2)_p$, wherein p is an integer ranging from 1 to 7; and R_6 is H; $(CH_2)_mH$; or $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8;

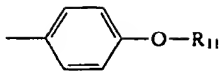
R_3 is selected from the group consisting of:





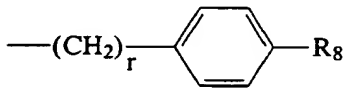


and



wherein q is an integer ranging from 1 to 8; D is selected from the group consisting of NH, S, and O; wherein R_7 is selected from the group consisting of H, OH, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; R_{11} is selected from the group consisting of $-CH_2COOH$ and $-CH_2\text{-}CONH(CH_2)_wNHZ$, wherein w is an integer ranging from 1 to 2 and Z is selected from the group consisting of hydrogen and acetate; and

R_4 is of the formula:



wherein R_8 is selected from the group consisting of H; OH; $(CH_2)_fNH_2$ wherein f is selected from the group consisting of 0 and an integer ranging from 1 to 8; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8.

2. The compound according to Claim 1, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is $(CH_2)_mOH$ wherein m is 2; R_7 is H; R_8 is NH_2; f is 0; n is 2; m is 2; q is 1; and r is 2.

3. The compound according to Claim 1, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is NH_2; R_8 is NH_2; f is 0; n is 2; q is 1; and r is 2.

4. The compound according to Claim 1, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is H; R_8 is NH_2; f is 0; n is 2; q is 1; and r is 2.

5. The compound according to Claim 1, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is H; R_8 is selected from the group consisting of $(CH_2)_sOH$ wherein s is 2 and $R_{10}COOH$, wherein R_{10} is CH=CH; n is 2; q is 1; and r is 2.

6. The compound according to Claim 1, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is selected from the group consisting of $(CH_2)_tOH$ wherein t is 2 and R_9COOH, wherein R_9 is CH=CH; R_8 is NH_2; f is 0; n is 2; q is 1; and r is 2.

7. An assay-type probe of the compound defined in Claim 1, wherein said assay-type probe is labeled with non-radioactive material.

8. The assay-type probe according to Claim 7, wherein said non-radioactive material is a fluorescent dye.

9. The assay-type probe according to Claim 7, wherein said non-radioactive material is biotin.

10. The assay-type probe according to Claim 7, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_7 is H; R_8 is NH_2; f is 0; n is 2; q is 1; r is 2; and R_6 is $(CH_2)_mOH$ wherein m is 2;

wherein said non-radioactive material is biotin bonded to the hydroxyl group present on R_6.

11. The assay-type probe according to Claim 7, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is NH_2; n is 2; q is 1; r is 2; and R_8 is NH_2; f is 0;

wherein said non-radioactive material is biotin bonded to the amino group present on R_8.

12. The assay-type probe according to Claim 7, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

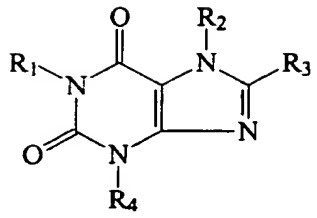
R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is H; n is 2; q is 1; r is 2; and R_8 is $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atoms;

wherein said non-radioactive material is biotin bonded to the carboxyl group present on R_8.

13. An assay-type probe of the compound defined in Claim 1, wherein said assay-type probe is labeled with radioactive material.

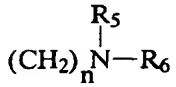
14. The assay-type probe according to Claim 13, wherein said radioactive material is a radioactive isotope selected from the group consisting of ^{18}F, ^{19}F, tritium, and ^{125}I.

15. A pharmaceutically acceptable salt of compound defined by the formula:



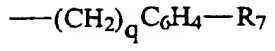
wherein R_1 is selected from the group consisting of C_1-C_8 alkyl;

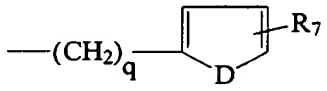
R_2 is of the formula:

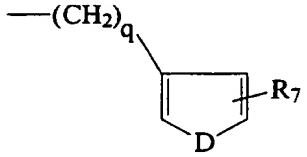


wherein n is an integer ranging from 1 to 8; R_5 is H or CH_3 $(CH_2)_p$, wherein p is an integer ranging from 1 to 7; and R_6 is H; $(CH_2)_mH$; or $(CH_2)_mOH$, wherein m is an integer ranging from 1 to 8;

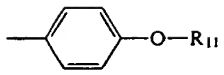
R_3 is selected from the group consisting of:





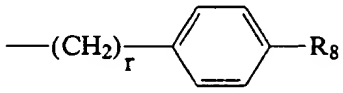


and



wherein q is an integer ranging from 1 to 8; D is selected from the group consisting of NH, S, and O; wherein R_7 is selected from the group consisting of H, OH, NH_2, R_9COOH, wherein R_9 is an alkylene or alkenylene group having 1 to 8 carbon atoms, and $(CH_2)_tOH$, wherein t is an integer ranging from 1 to 8; R_{11} is selected from the group consisting of $-CH_2COOH$ and $-CH_2$-$CONH(CH_2)_wNHZ$, wherein w is an integer ranging from 1 to 2 and Z is selected from the group consisting of hydrogen and acetate; and

R_4 is of the formula:



wherein R_8 is selected from the group consisting of H; OH; $(CH_2)_fNH_2$ wherein f is selected from the group consisting of 0 and an integer ranging from 1 to 8; $(CH_2)_sOH$, wherein s is an integer ranging from 1 to 8; and $R_{10}COOH$, wherein R_{10} is an alkylene or alkenylene group having 1 to 8 carbon atoms; and r is an integer ranging from 1 to 8.

16. The compound according to Claim 15, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is $(CH_2)_mOH$ wherein m is 2; R_7 is H; R_8 is NH_2; f is 0; n is 2; m is 2; q is 1; and r is 2.

17. The compound according to Claim 15, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is NH_2; R_8 is NH_2; f is 0; n is 2; q is 1; and r is 2.

18. The compound according to Claim 15, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is H; R_8 is NH_2; f is 0; n is 2; q is 1; and r is 2.

19. The compound according to Claim 15, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is H; R_8 is selected from the group consisting of $(CH_2)_sOH$ wherein s is 2 and $R_{10}COOH$, wherein R_{10} is CH=CH; n is 2; q is 1; and r is 2.

20. The compound according to Claim 15, wherein R_1 is C_3 alkyl; R_3 is:

$$—(CH_2)_qC_6H_4—R_7$$

R_5 is CH_3 $(CH_2)_p$ wherein p is 1; R_6 is H; R_7 is selected from the group consisting of $(CH_2)_tOH$ wherein t is 2 and R_9COOH, wherein R_9 is CH=CH; R_8 is NH_2; f is 0; n is 2; q is 1; and r is 2.

21. A pharmaceutical composition which comprises a compound of Claim 1 and a pharmaceutically acceptable carrier.

INTERNATIONAL SEARCH REPORT

Inte onal Application No
PCT/US 97/21045

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D473/06 A61K31/52 G01N33/06 G01N33/60

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D G01N A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	BE 636 828 A (MANUFACTURE DE PRODUITS PHARMACEUTIQUES A. CHRISTIAENS S.A.) 2 March 1964 see the whole document	1-6
P,A	EP 0 764 647 A (BAYER AG) 26 March 1997 see the whole document	1-6
A	EP 0 501 379 A (KYOWA HAKKO KOGYO CO.,LTD) 2 September 1992 see page 2, line 7 - line 10	1-6
A	EP 0 503 563 A (MERRELL DOW PHARMACEUTICALS) 16 September 1992 see page 2, line 5 - line 8	1-6

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

1

Date of the actual completion of the international search	Date of mailing of the international search report
13 March 1998	07/04/1998

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Form PCT/ISA/210 (second sheet) (July 1992)

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information on patent family members

Inte onal Application No
PCT/US 97/21045

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